A Simple Method to Model a Continuous Glucose Monitoring Signal

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Abstract: Before continuous glucose monitoring (CGM) can be safely used to guide glycaemic control (GC) protocols the impact of suboptimal accuracy resulting from error or delay in calibration measurement, sensor drift, and delayed glucose diffusion must first be characterised. Characterising this error allows models to be formed so in-silico simulations can test the performance and safety of CGM driven glycaemic control protocols and examine best and worst scenarios. Existing models of CGM dynamics are now 10 years old and significant advances in sensor technology mean the level of error produced by these models no longer characterises the dynamics of more recent CGM devices. Therefore, this paper presents and validates a simple CGM error model based on the latest available CGM devices, as well as a generalisable sensor modeling approach.

The model was created using 28 data sets from an observational pilot study of CGM in patients admitted to the Christchurch Hospital ICU during 2014-15. The model was characterised by empirical models of drift and noise. Autocorrelation was then used to validate the modelled data with the measured data. The median absolute difference between modelled and measured SG autocorrelation values was 0.007 with a range of 0 – 0.13. Hence, the model is judged to be suitable for use in simulation to provide better insight into using CGM to guide GC will effect control and its safety and performance. The overall modelling process is data driven and readily generalised to any other device.

Keywords: Developments in measurement, signal processing, Identification and validation, Error quantification, Time series modelling, Healthcare management, disease control, critical care

1. INTRODUCTION

Two in-silico studies (Signal et al., 2010, Mombaerts et al., 2015) and a recent pilot observational trial (Signal et al., 2013) have shown that continuous glucose monitoring (CGM) devices, when coupled with a well-designed glycaemic control (GC) protocol, offer several potential benefits over the standard practice of intermittent blood glucose (BG) monitoring. These studies have shown CGM devices have the ability to reduce hypoglycaemia, maintain BG control, and reduce nurse workload.

Typical glycaemic control protocols require BG measurements every 1-4 hours (Evans et al., 2012, Lonergan et al., 2006, Plank et al., 2006, Blaha et al., 2009), typically resulting in ~6 - 14 blood draws a day per patient. This frequency can represent a measurable part of total nurse workload (Carayon et al., 2005, Holzinger et al., 2005). CGM devices have the potential to drastically reduce the number of BG measurements per day, positively impacting workload, while also improving patient safety and increasing time in the desired BG target band.

However, CGM devices tend to have suboptimal accuracy resulting from error or delay in calibration measurement, sensor drift, and delayed glucose diffusion (O'Sullivan et al., 2007, Heath et al., 1983). Thus, before CGM can become ubiquitous in the care of critically ill patients these errors on BG control must first be quantified and understood. Subsequently, their interaction with GC protocols and resulting impact on performance and safety can be assessed.

Despite significant outpatient use and promise for CGM (Breton et al., 2008, Klonoff, 2005a, Klonoff, 2005b) the literature contains very few reports of error models derived from clinical sensor glucose (SG) data. Without a good model of CGM dynamics the feasibility of CGM combined with GC cannot be assessed in-silico. Two studies have provided sufficient details of CGM device error characteristics to allow models to be created or reproduced for use in-silico (Breton et al., 2008, Goldberg et al., 2004). However, these models are now 10 years old and significant advances in sensor technology mean the level of error produced by these models no longer characterises the dynamics of more recent CGM devices. Therefore, this paper presents and validates a simple CGM error model based on the latest available CGM devices.

2. PATIENTS & METHODS

2.1 Patients

This study uses data from an observational pilot study of CGM in patients admitted to the Christchurch Hospital ICU during 2014-15. All patients were recruited by a physician in the ICU and informed written consent obtained. If the patient was unable to consent next of kin were approached for consent and follow up consent was obtained from the patient at a later date if applicable. Inclusion criteria were:

- Two consecutive BG measurements greater than

8 mmol/L, indicating the need for insulin therapy using the STAR protocol (Evans et al., 2012)
- Expected admission of at least 3 days
- Over 18 years of age
- A platelet count > 30,000/mL.

Patients were excluded if they were not expected to survive, receiving hydroxyurea, pregnant, and/or lacked clinical equipoise. This study and use of data was approved by the Upper South A Regional Ethics Committee, New Zealand (URA/12/02/004). Table 1 shows the patient demographics.

Table 1. Patient demographics displayed as median [IQR] where appropriate. APACHE II = Acute Physiology and Chronic Health Evaluation II.

Patients	21
Ages (years)	60 [55 – 68]
Sex (M/F)	11/9
APACHE II score	20 [16 – 25]
Outcome (L/D)	14/7

All patients were monitored for a period of up to 3 days using the Sentrino monitoring system (Medtronic, MiniMed, Northridge, California). Patients had either one abdomen and one thigh sensor, two abdomen sensors, or one thigh sensor inserted by a trained clinician, depending on which trial phase they were enrolled in. Calibration BG measurements were obtained by specifically trained ICU nurses at least 3 times per day as recommended by the device manufacturer (MiniMed, 2014). BG measures were obtained using the Roche Accu-chek Inform II (F. Hoffmann-La Roche Ltd, Basle, Switzerland) hospital grade glucose meters as is standard practice in the Christchurch ICU, with blood typically obtained from an arterial line. CGM devices were strictly not used for determining treatment for GC during this study.

In addition to BG measurements used for calibration of SG data, each patient had intermittent BG monitoring every few hours. The STAR protocol requires, on average, 12-14 BG measurements per day to guide insulin/nutrition therapy (Fisk et al., 2012). These additional reference measurements can be used to assess CGM accuracy.

Each SG signal was treated separately for modelling purposes. Three patients were excluded from the analysis, Patients 17, 21 and 24. These patients had early sensor failure and were deemed clinically unsuitable for replacement sensors. In each case, not enough data was collected from these patients to be relevant to the model. Additionally, any data characteristic of a failed sensor or uncharacteristic of a sensor signal was removed, shown in Appendix A. This removal resulted in 28 separate SG signals for analysis. Table 2 summarises the data used for modelling and validation.

Table 2: Data used for modelling and validation

No. SG signals	28
No. SG hours	1689
No. Calibration measurements	380
No. Reference measurements	669

2.3 Model development

The error in a CGM signal can be broken down into separate parts specifically, the true BG signal noise and drift:

$$CGM = BG_{real} + noise + drift \qquad (1)$$

Where noise is the random error centred about 0 and drift is a linear bias between calibration measurements. Noise and drift were modelled based on clinical Sentrino data to create a CGM model with outputs added to reference blood glucose values to simulate the impact of CGM error on GC results.

A constant drift rate with a linear bias, was assumed for the drift model, based on clinical observation and prior data. Drift was defined as the rate of increase in discrepancy between CGM signal and calibration BG measurements. The drift profile between any two calibration BG measurements was then defined by *delta*, the accumulated drift magnitude. The magnitude of accumulated drift between any two calibration BGs was found by measuring the size of the bias (CGM value – Calibration BG) at the second calibration BG as shown in Figure 1. Once *delta* is identified for each calibration measurement it can be removed from the SG for further analysis. This calculation resulted in a new drift-corrected CGM profile as shown in Figure 1.

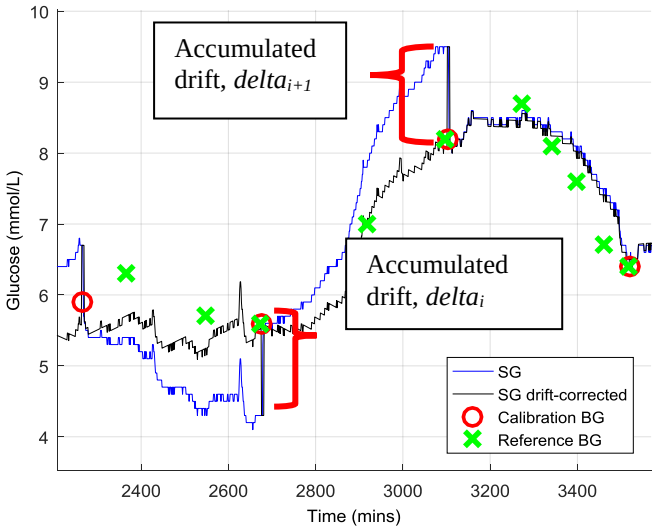

Fig 1. Example of accumulated drift in a SG signal and a SG signal once drift is removed

The sections between each calibration measurement were considered independently because calibration should correct for any drift. Autocorrelation of the delta data shows no tendency for a sensor to repeatedly drift in the same direction, as shown in Figure 2. Autocorrelation is the dot product of the signal after it has been shifted in time by some amount. The resultant angle, θ, shows the trend similarity between two vectors and its cosine has values from -1 and +1 demonstrating opposing to complete agreement. A lag window of up to 10 minutes was considered. Therefore, the similarity of the signal to itself was compared every minute from 10 minutes before to 10 minutes after the current time. The *delta* data was first

mean shifted before autocorrelation was applied to remove bias.

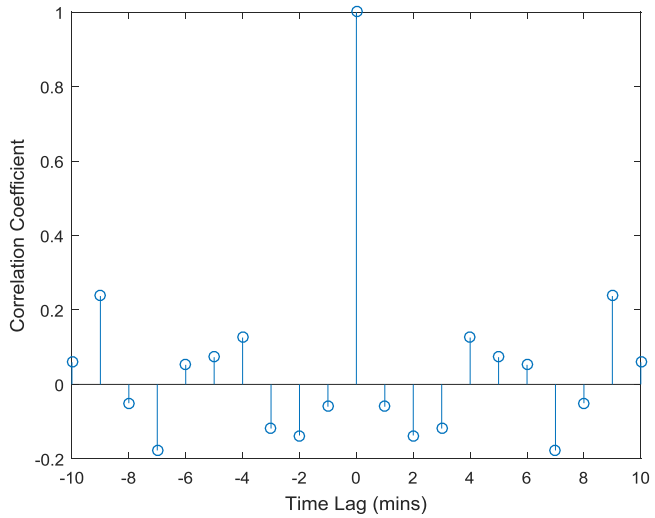

Fig 2. The autocorrelation of the delta drift data over a lag window of +10 and -10 minutes, for all data points. There is no correlation evident within this window.

An empirical model of drift was implemented from the cumulative distribution function (CDF) of the *delta* data across the entire cohort using inverse transform sampling. This method is implemented by interpolating the CDF to 100,000 points to ensure a smooth curve. A uniform random number generator then selects a value in the range 0 – 1 which was then used to obtain the corresponding interpolated CDF delta value. The process can be repeated resulting in a dataset that has the same distribution as per the empirical data.

Sensor noise contributes the remaining zero mean, random error to the modelled CGM signal of Equation 1. Noise was split into two components, low and high frequency noise. Low frequency noise is considered "the long duration" sensor noise, or, in this case, the difference between reference BG and the SG once drift is removed. High frequency noise is the "minute to minute" noise that gives the SG signal a jagged appearance.

The low frequency noise was considered to be the difference between each independent reference BG and the drift-corrected SG signal. Low frequency noise accounts for the error that occurs intermittently over longer time periods, which could be induced by events such as turning or other accidental pressure applications on the sensor site (Helton et al., 2011a, Helton et al., 2011b). As was done for the drift data, an empirical model was generated from a CDF of low frequency noise by inverse sampling.

Unlike low frequency sensor noise, high frequency sensor noise occurs minute-to-minute and results in the 'jagged' appearance of the CGM signal. High frequency noise represents electrical noise, random variation induced by the imperfect reading and transmission of the sensor signal. High frequency noise is very small in magnitude thus does not affect the identification of low frequency noise. A simple model was created using the CGM data by calculating the size of the changes in glucose from sample to sample (every minute). The sample-to-sample change was then halved to obtain an amplitude because noise is assumed to be zero mean so sample-to-sample changes would double the amplitude found over many measurements. Thus, it yields an independent, random added noise with sample-to-sample changes similar to those observed in the empirical data.

2.4 Model development

To ensure the CGM model produced similar dynamics to the CGM sensors, the 28 data sets containing true reference and calibration BGs provided the framework to generate modelled SG signals. The reference and calibration BGs were linearly interpolated to give a 'true BG signal'. CGM drift, and noise are added to this 'true BG signal', as shown in subplot A of Figure 3.

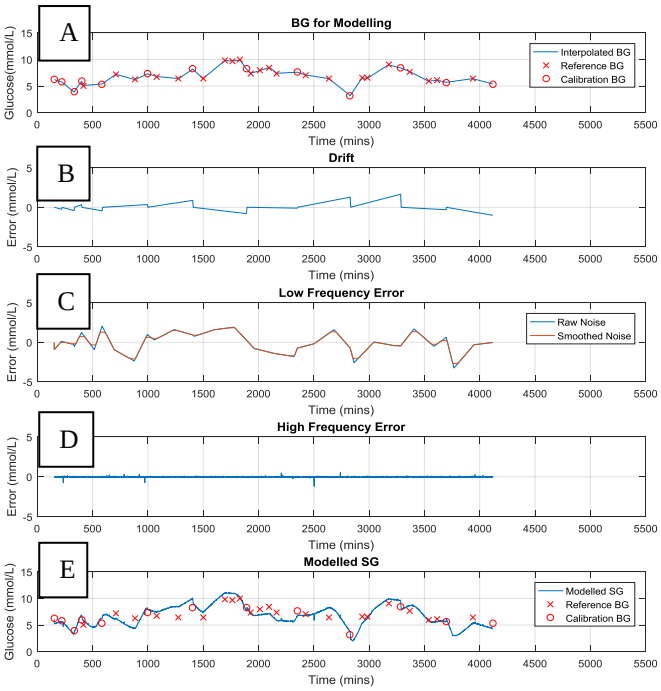

Fig 3. Example of the process undertaken to model a SG signal. First the BG measurements are interpolated, A. Then drift, low frequenacy and high frenquency error are found by sampling from their emperical distributions, B, D and C respectively. Finally, the error is added to the interpolated BG to prove the simulated signal, E.

A drift profile was then created using the empirical drift model to randomly generate a drift *delta* value for each 8 hour calibration interval, as shown in subplot B of Figure 3. A low frequency noise profile created by sampling every 160 minutes from the low frequency error model. Samples were taken at 160 min intervals as opposed to at the time of reference BG measurements because some data sets contained infrequent reference BG measurements and the mean reference measurement interval across the available dataset was 160 minutes. Consecutive samples were linearly interpolated and a median filter was used to smooth the error signal, as shown in subplot C of Figure 3, where the median filtering removes the

uncharacteristic sharp edges introduced by the linear interpolation between the error points. Finally, a high frequency noise profile was generated every minute by randomly sampling from the empirical high frequency model, as shown in subplot D of Figure 3. The summed result of each component yields a simulated true BG with CGM error, as shown in Figure 3 subplot E.

The overall model development method is general and data driven. The use of drift and random errors is general, as these can occur in any such device, and if they don't, they are essentially set to zero by their absence. Thus, given data from another sensor, a similar model could be generated and similarly tested and validated.

2.5 Model Validation

The CGM model is a created using random process. Therefore, it cannot be deterministically compared to actual measured CGM data and, importantly, no two uses of the model for the same true BG data yield the same result. Thus, to validate the modelled signals, autocorrelation was used to assess the similarity of the simulated CGM signals to the original CGM data.

All signals were first mean shifted to remove bias before autocorrelation was applied. If the resulting autocorrelation coefficients of the simulated SG and real SG are similar then the model can be considered to provide a realistic approximation of the sensor dynamics. The auto-correlation coefficients can be statistically assessed over several runs of the model for any given real SG trace.

A total of 50 model-derived SG signals were simulated for each patient and the autocorrelation coefficient was calculated between the real SG and each simulated SG signal over a +10 mins to -10 mins window. The median and range of correlation coefficients of the modelled SG was then compared to the correlation coefficient of the measured SG. The closer the agreement between the correlation coefficients of the simulated signals, and the correlation coefficient of the real CGM signal the better the model.

3. RESULTS & DISCUSSION

Visually and qualitatively, the CGM model generates similar signals to the empirical data. An example signal is shown in Figure 4 with real SG and 3 simulated signals. In particular, it is difficult to distinguish the real CGM signal from the modelled signals.

Figure 5 displays the median and range of autocorrelation values for each time lag for each patient's modelled SG signals. The modelled SG show very similar autocorrelation trends to those displayed by the measured data. Measured SG is less tightly correlated than the median modelled SG in the majority of cases. However, only 3/28 measured SG values (A, B and C in Figure 5) do not sit within the range of modelled SG across all of the 20 minute (+/- 10 minute) windows and the median difference between the modelled and measured SG correlation values was 0.007 with a range of 0 – 0.13, the biggest differences occurring at the +10 or -10 minute time shift, where correlation might generally be expected to be weaker given the time difference from the original model.

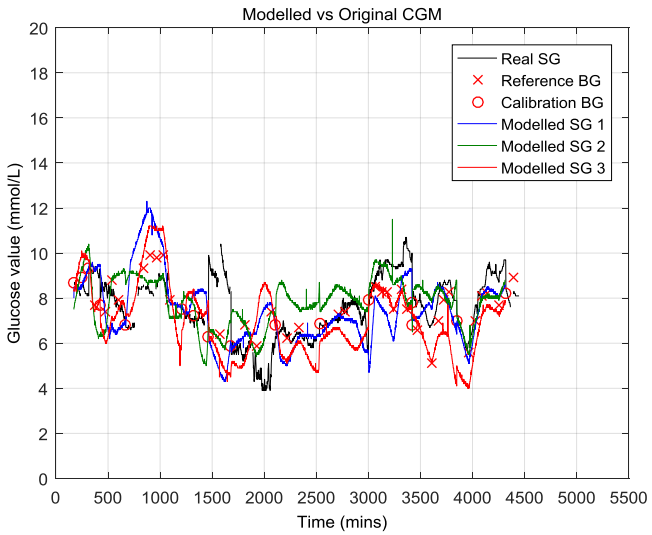

Fig. 4. Comparing the original SG signal to that of three different modelled signals using the CGM modelled generated from empirical data

The SG of the three instances (A, B and C in Figure 5) where the measured SG autocorrelation does not fall within the range of modelled SG autocorrelation for all time lags are shown in Figure 6. It is evident the lack of agreement is most likely due to individual cases where the sensor did not behave as expected. Thus, in these limited cases, the behaviour of the sensor as seen in the data cannot be easily explained by the noise and error types defined.

In this figure, subplot A corresponds to the A in Figure 5 and the high frequency noise has increased noticeably about halfway through the signal which is not seen in any of the other 28 SG signals. Subplot B corresponds to the SG of Figure 6B. The sensor glucose has many small unusual spikes uncharacteristic of the other sensors. Subplot C corresponds to Figure 6C where there is a large drop out at 300 minutes in SG compared to an otherwise stable signal with some strange spikes.

Additionally, over all patients sensor glucose is very tightly correlated in both measured and modelled SG. This result is logical as the rate of which blood glucose can change is physiologically limited and under normal conditions blood glucose will be related over a short time period, such as 10 minutes. However, if the time lag is extended to ±20 or ±30 minutes the correlation coefficients of both the modelled SG and measured SG reduce, as expected.

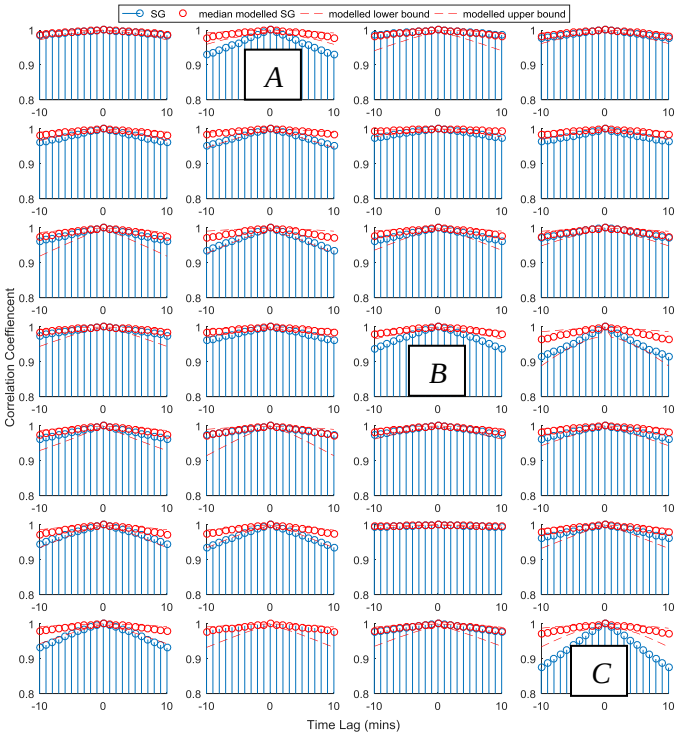

Fig 5. Comparing the autocorrelation coefficients for the real SG to the median and range correlation coefficients of the modelled SG. A, B, and C are where the measured SG autocorrelation does not fall within the range of modelled SG autocorrelation.

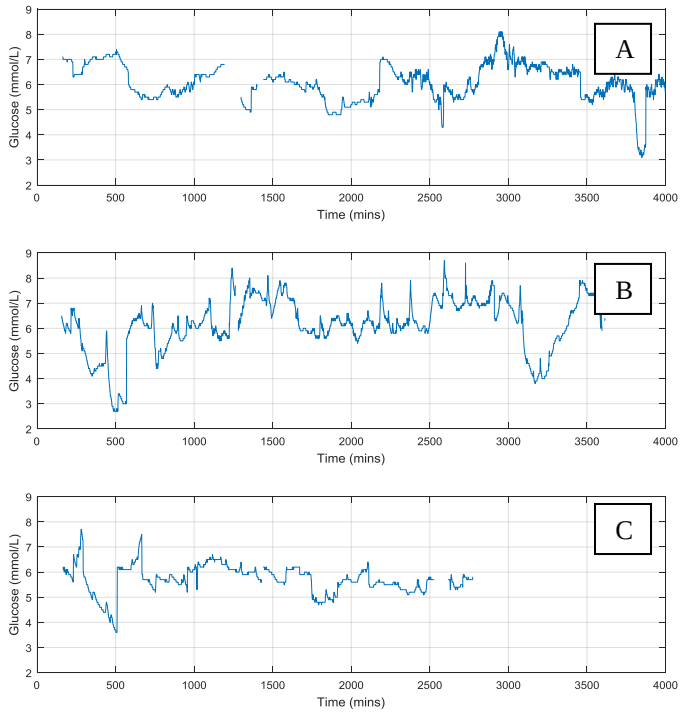

Fig 6. The sensor glucose for the three instances where the autocorrelation range of the modelled SG does not include the autocorrelation of the measured SG for all time lags. A, B and C correspond to the A, B and C of Figure 5.

3.1 Limitations

This analysis is limited by only have 28 data sets to generate the model from. A larger cohort would provide more data to generate the empirical models from. However, the consistency of the autocorrelation coefficients of the simulated signals to the real SG value indicates there is enough data to provide an acceptable model. Equally, as more data is aggregated from any given sensor type in use, the modeling methodology is more than general enough to be updated as required,

Notably, the same updating approach would also apply as sensors improve over different design changes and sensor generations. An equally applicable aspect of the model and its ability to update would include the ability to see, by tracking sensor data in use, if sensor performance changed, for better or worse. Such changes can occur, for one example, due to changes in design or manufacturing that impact sensor performance directly or in clinical use.

A further limitation is the limited choice of noise/error types. However, the 3 choices cover most variations observed clinically without adding extra complexity and unnecessary dynamics. Finally, this model is limited by the fact it is data driven, not a dynamic, deterministic model. The benefits of this method are that it simplifies the process of calculating exact dynamic and electronic, physiological and other noise causes/sources.

3. CONCLUSIONS

The CGM error model generated using the Sentrino data provides a realistic SG signal. Only 3 of 28 measured SG values do not sit with in the range of modelled SG across the entire 20 minute window considered. The median absolute difference between modelled and measured SG autocorrelation values was 0.007 with a range of 0 – 0.13. Hence, the model is judged to be suitable for use in simulation to provide better insight into using CGM to guide GC will effect control and its safety and performance. The overall modelling process is data drive and readily generalised to any other CGM.

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Appendix A. FIRST APPENDIX

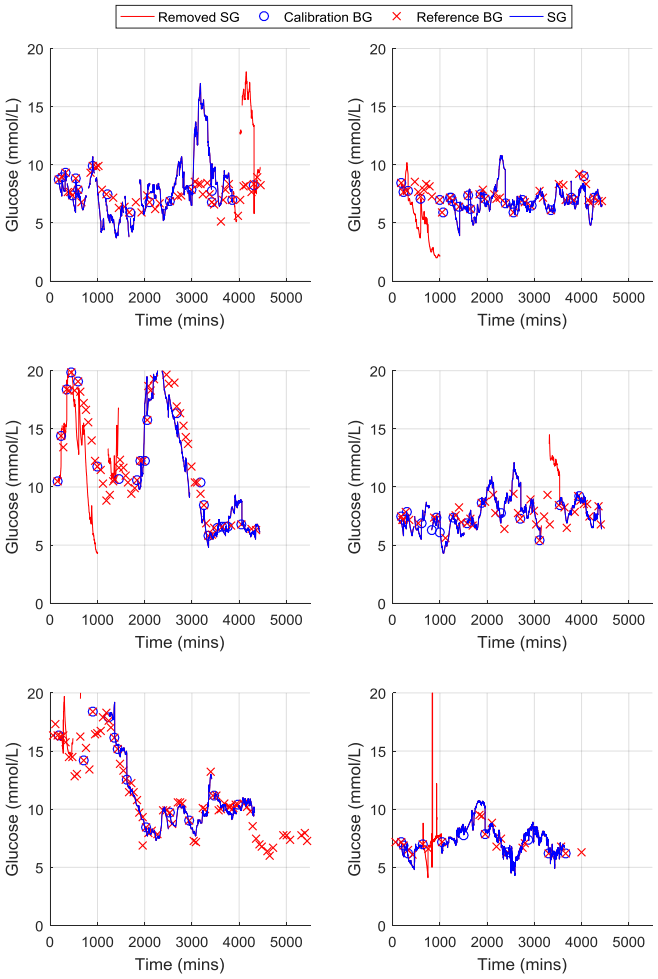

Fig A1. The sensor glucose that was removed from 6 patients data due to being uncharacteristic of the sensor, most commonly as the result of sensor failure.